

Clinical Factors Associated With Failed Weaning From Intraoperative Extracorporeal Membrane Oxygenation Used During Lung Transplantation

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) promotes adequate oxygenation and hemodynamic stability during lung transplantation (LTx). However, some recipients cannot be weaned from ECMO following surgery. Thus, we evaluated the prognosis and risk factors of failed weaning from intraoperative ECMO during LTx.

Methods: We retrospectively analyzed data from 274 patients receiving intraoperative ECMO during LTx. Risk factors were evaluated using logistic regression analyses.

Results: Weaning failure occurred in 118 patients (43.1%). Intensive care unit stay was longer and mortality was higher in the failed weaning group than in the successful weaning group. The failed weaning group exhibited significantly older donor age, lower donor PaO₂/FiO₂ ratio, greater intraoperative transfusion volume, and longer operation time than the successful weaning group. Recipient age, body mass index, donor age, lower donor PaO₂/FiO₂ ratio, donor/recipient total lung capacity (TLC) ratio, greater intraoperative transfusion volume, and longer operation time were associated with weaning failure after adjustment.

Conclusion: The failed weaning group showed a poor prognosis. Perioperative factors including donor age, donor PaO₂/FiO₂ ratio, donor/recipient TLC, operation time, and blood loss can predict postoperative ECMO weaning failure.

Background

Lung transplantation (LTx) is an established treatment option for patients with a variety of end-stage lung diseases. The number of LTx procedures performed has rapidly increased due to advancements in operative techniques such as extracorporeal membrane oxygenation (ECMO) [1, 2].

During LTx surgery, cardiopulmonary bypass (CPB) is used for cardiopulmonary support to prevent hemodynamic compromise due to single-lung ventilation, pulmonary artery clamping, and heart manipulation [3-5]. However, the use of CPB during LTx is debated, and recent studies from several LTx centers have reported favorable results using ECMO as an alternative to CPB [1, 6].

Previous studies have indicated that intraoperative ECMO is associated with a shorter intensive care unit (ICU) stay, less bleeding, fewer reoperations, and less primary graft dysfunction than CPB [7, 8]. Our institution also uses intraoperative ECMO instead of CPB, and we have routinely used it during LTx since 2013 [6].

However, some recipients cannot be weaned from ECMO following surgery due to hemodynamic instability, early graft failure, infection, or acute rejection. Survival outcomes among patients receiving ECMO well into the postoperative period vary according to issues necessitating ECMO, such as primary graft dysfunction, high pulmonary vascular resistance, pneumonia, and sepsis [9-15]. Mason *et al.*

revealed that the mortality risk was higher among patients receiving ECMO support after LTx than among those not receiving support; however, there was no difference in survival beyond 1 year between the two groups [16].

Several studies have analyzed risk factors and survival rates among patients who underwent LTx with planned postoperative extended ECMO due to severe pulmonary hypertension (PH) [9, 10, 17]. To the best of our knowledge, few studies have focused on factors associated with prolonged intraoperative ECMO after LTx [1, 18]. Therefore, we aimed to investigate the prognosis of patients who continued to receive ECMO support following LTx and the risk factors for weaning failure from intraoperative ECMO in these patients.

Methods

Study design and population

In this single-center retrospective study, we reviewed data from consecutive patients who underwent LTx at Severance Hospital in South Korea from October 2012 to September 2020. Patients who underwent multi-organ transplantation (lung-liver, n=2; lung-kidney, n=2; heart-lung, n=1), those who did not receive intraoperative ECMO (CPB, n=6), those who underwent re-transplantation (n=5), and those aged ≤ 18 years (n=4) were excluded from the study. The remaining 274 patients were divided into two groups based on the success or failure of weaning from intraoperative ECMO immediately following LTx.

All LTx procedures were performed under ECMO support. Most patients received femoro-femoral venoarterial ECMO unless bridging ECMO was required during the waiting period. Weaning from ECMO was attempted post-surgery, following which patients were transferred to the ICU. The decision to wean from ECMO was determined according to the patient's status after reducing ECMO flow to 0.5 L/min. Under conditions of hemodynamic instability, such as (a) the need for a high-dose vasopressor, (b) decreased cardiac function based on transesophageal echocardiography, or (c) systolic blood pressure < 100 mmHg despite treatment with norepinephrine (> 0.2 $\mu\text{g}/\text{kg}/\text{min}$) and vasopressin (> 0.05 U/min), venoarterial ECMO was maintained. Furthermore, ECMO support (veno-venous) was maintained despite hemodynamic stability if $\text{PaO}_2/\text{FiO}_2$ was < 150 mmHg with a positive end-expiratory pressure of 8 cmH_2O . Conversely, ECMO support was removed when hemodynamic stability and the target saturation were achieved.

All patients underwent induction immunosuppression therapy with high-dose corticosteroids (methylprednisolone at 250 mg during the operation and 0.5 mg/kg/day for 3 days after the operation). Triple immunosuppression therapy (e.g., prednisolone, tacrolimus, and mycophenolate mofetil) was used to maintain immunosuppression after transplantation. Patients who received bridging ECMO from January 2019 onward received 20 mg of basiliximab during transplantation surgery and were initiated on tacrolimus after 7 days. Ganciclovir and itraconazole were used in all recipients until 6 months

postoperatively. Lifelong trimethoprim/sulfamethoxazole was used in all recipients to prevent *Pneumocystis jirovecii* after LTx.

Data collection for determining risk factors of failed weaning from intraoperative ECMO

All data were collected from the electronic medical records of the hospital. Baseline data prior to LTx including demographic characteristics, cardiac function, comorbidities, and status while waiting were collected. Operative data included operation time, input and output of fluid and blood, and ischemic time in the donor lung. Additionally, data related to the donor's demographics, PaO₂/FiO₂ on the day of donation, and the time of mechanical ventilator application in the donor lung were collected.

Ethical approval

This research protocol was approved by the Institutional Review Board of Severance Hospital, South Korea (IRB No. 4-2021-0199), and the study design was approved by the appropriate ethics review boards. The requirement for obtaining patient informed consent was waived due to the retrospective nature of the study.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 25.0 (IBM Corporation, Armonk, NY). Continuous data are expressed as mean±standard deviation, and categorical data are expressed as numbers with corresponding percentages. Continuous and categorical variables were analyzed using Student's *t*-tests and chi-square/Fisher's exact tests, respectively.

A multivariate logistic regression model was used to identify independent risk factors for prolonged intraoperative ECMO. The model included variables with a level of significance <0.05 in the bivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For some continuous data, receiver operating characteristic (ROC) analysis was used to determine the cut-off value using the area under the curve (AUC). Survival data were estimated using the Kaplan–Meier method, and significant differences were determined using the log-rank test. Statistical significance was set at $p<0.05$.

Results

Study population

During the study period, 294 patients underwent LTx. Of these, 274 were enrolled for analysis. The mean patient age was 54.6±11.4 years, and 63.9% of patients (n=175) were male. The major reason for LTx was idiopathic pulmonary fibrosis (n=149, 54.4%), followed by connective tissue disease-associated interstitial lung disease (n=49, 17.9%). During the LTx waiting period, 65.7% (n=180) of the enrolled patients were in the ICU, and 31% (n=85) received bridging ECMO. Immediately following the operation, 118 patients (43.1%) were admitted to the ICU while maintaining ECMO (Supplementary Table 1).

Comparison between the successful and failed weaning groups after LTx

Among the enrolled patients, 118 (43.1%) were not weaned from ECMO, while 156 (56.9%) were successfully weaned from ECMO after the operation. Table 1 shows the results of the comparison between the two groups. The proportion of female patients and body mass index (BMI) were significantly higher in the failed weaning group than in the successful weaning group (female sex, 43.2% vs. 30.8%, $p=0.034$; BMI, 21.7 ± 4.1 vs. 20.4 ± 4.0 kg/m², $p=0.009$). Perioperatively, the failed weaning group exhibited longer operation times, a larger amount of blood loss, and higher fluid intake and transfusion volumes than the successful weaning group (mean operation time, 513.9 vs. 479.8 min, $p=0.001$; blood loss, 3.4 vs. 2.7 L, $p=0.030$; fluid intake, 12.1 vs. 10.2 L, $p=0.011$, transfusion volume, 3.4 vs. 2.7 L, $p=0.027$). Among donor-related variables, there were significant differences in age, PaO₂/FiO₂ ratio, and predicted donor/recipient total lung capacity (TLC) ratio between the two groups. Donors were significantly older in the failed weaning group than in the successful weaning group (44.7 vs. 41.9 years, $p=0.014$). The PaO₂/FiO₂ ratio of the donor lung was significantly lower in the failed weaning group than in the successful weaning group (432.6 vs. 472.8, $p<0.001$), while the predicted donor/recipient TLC was higher (110.1 vs 105.2%, $p=0.034$).

Prognosis according to the success of intraoperative ECMO weaning

The failed weaning group exhibited a significantly longer ICU stay and duration of hospitalization after LTx than the successful weaning group (length of ICU stay, 24.5 vs. 9.0 days, $p<0.001$; length of hospitalization: 82.5 vs. 63.6 d, $p=0.023$, respectively). The mortality rates at 6 months and 1 year were significantly higher in the failed weaning group than in the successful weaning group (6 months, 29.7 vs 17.9%, $p=0.023$, 1 year, 43.2 vs. 26.8%, $p=0.005$). An analysis of overall survival during the observation period (October 2012 to May 2021) revealed that mortality rates were higher in the failed weaning group than in the successful weaning group ($p=0.002$, Figure 1).

Table 1. Comparison of data between the patients weaned successfully from ECMO and those who remained with ECMO support after lung transplantation

Variables	ECMO after LTx (n=118)	No ECMO after LTx (n=156)	p-value
Age, years	53.6 ± 11.8	55.4 ± 11.1	0.218
Male sex	67 (56.8)	108 (69.2)	0.034
Body mass index, kg/m ²	21.7 ± 4.1	20.4 ± 4.0	0.009
Single lung transplantation	6 (5.1)	5 (3.2)	0.539
Cause of LTx			0.012
IPF	60 (50.8)	89 (57.1)	
CTD ILD	27 (22.9)	22 (14.1)	
BE	4 (3.4)	13 (8.3)	
LAM	2 (1.7)	3 (1.9)	
COPD	1 (0.8)	9 (5.8)	
BO	6 (5.1)	10 (6.4)	
Others	18 (15.3)	11 (6.8)	
Hypertension,	26 (22)	39 (25)	0.568
Diabetes mellitus	31 (26.3)	48 (30.8)	0.416
Mean PAP, mmHg (46/58 missing)	28.5 ± 12.9	27.1 ± 9.3	0.423
Pulmonary hypertension (50/60 missing)	38 (55.9)	57 (58.2)	0.770
ICU care before LTx	80 (67.8)	100(64.1)	0.524
ICU waiting time, days	24.5 ± 80.5	15.2 ± 20.3	0.167
Mechanical ventilation before LTx	53 (44.9)	52 (33.3)	0.051
ECMO before LTx	43 (36.4)	42 (26.9)	0.092
Operation			
Operation time, min	513.9 ± 89.1	479.8 ± 73.5	0.001
Operation time > 470 min	84 (71.2)	77 (49.4)	<0.001
Ischemic time, Right lung, min	236.5 ± 85.6	229.4 ± 71.7	0.460
Ischaemic time, Left lung, min	336.1 ± 86.7	322.6 ± 78.0	0.186
Total fluid input, millilitres	12164.3 ± 7115.7	10245.1 ± 4443.6	0.011
Total fluid output, millilitres	5246.5 ± 3982.9	4356.6 ± 3314.8	0.051

Difference between Input and output	6704.7 ± 5162.0	5867.1 ± 2674.2	0.085
Red blood cell transfusion	3416.0 ± 2719.6	2727.7 ± 2239.0	0.027
Blood loss	3629.7 ± 3347.7	2793.2 ± 2797.2	0.030
Postoperative outcome			
ICU care after LTx, days	24.5 ± 31.8	9.0 ± 8.9	<0.001
HD after LTx, days	82.5 ± 72.0	63.6 ± 79.5	0.045
Six-month mortality	35 (29.7)	28 (17.9)	0.023
One-year mortality* (without within 1 yrs)	48 (43.2)	41 (26.8)	0.005
Donor			
Age, years	44.7 ± 12.2	41.0 ± 12.6	0.014
Male sex	73 (61.9)	90 (57.7)	0.486
Mechanical ventilation, hours	161.5 ± 116.6	157.8 ± 100.2	0.779
Donor PaO ₂ /FiO ₂ ratio	432.6 ± 85.0	472.8 ± 90.4	<0.001
Donor/recipient TLC ratio, %	110.1 ± 21.3	105.2 ± 16.5	0.034
pTLC <80, >120	33 (28)	37 (23.7)	0.425

Values are expressed as means (standard deviations) or median (interquartile ranges).

ECMO, extracorporeal membrane oxygenation; LTx, lung transplant; IPF, idiopathic pulmonary fibrosis; CTD ILD, connective tissue disease interstitial lung disease, BE; bronchiectasis; LAM, Lymphangioliomyomatosis; COPD, chronic obstructive pulmonary disease; BO, Obliterative bronchiolitis; others, NSIP (Non-specific interstitial pneumonia), PPFE (Pleuroparenchymal fibroelastosis), ARDS (Acute Respiratory Distress syndrome), AFOP (Acute fibrinous and organizing pneumonia); mean PAP, mean pulmonary artery pressure; ICU, intensive care unit; HD, hospital day; PaO₂/FiO₂, ratio of arterial oxygen concentration to the fraction of inspired oxygen; TLC, total lung capacity

Risk factors for failed weaning from intraoperative ECMO immediately after LTx

Univariate analysis revealed that sex, BMI, donor age, PaO₂/FiO₂ ratio in the donor lung, predicted donor/recipient TLC, intraoperative blood loss, and operation time were risk factors for failed weaning from intraoperative ECMO (Supplementary Table 2). A multivariate analysis including variables identified as significant in the univariate analysis identified age, BMI, transfusion volume >3.8 L, donor age, PaO₂/FiO₂ ratio in the donor lung, and predicted donor/recipient TLC as independent risk factors for intraoperative ECMO weaning failure (Table 2).

Table 2. Risk factors of failed ECMO weaning after lung transplantation

Variables	Multivariate*		
	OR	CI	p-value
Age	0.969	0.945-0.994	0.014
Body mass index	1.122	1.042-1.207	0.002
Operation time > 470 min	1.768	0.983-3.179	0.057
Transfusion during Op > 3.8 liters	2.825	1.434-5.567	0.003
Donor age, year	1.029	1.007-1.052	0.010
Donor PaO ₂ /FiO ₂ ratio	0.994	0.991-0.997	<0.001
Donor/recipient TLC ratio	1.019	1.003-1.036	0.017

OR, odds ratio; CI, confidence interval; PaO₂/FiO₂, ratio of arterial oxygen concentration to the fraction of inspired oxygen; TLC, total lung capacity. *The multivariable logistic regression model was done by adjusting for age, sex, body mass index, donor age, donor PaO₂/FiO₂ ratio, donor/recipient TLC ratio, mechanical ventilation before LTx, transfusion during operation, and operation time.

Analysis of risk factors for intraoperative ECMO weaning failure among patients receiving bridging ECMO while waiting for LTx

Since bridging ECMO prior to LTx can affect intraoperative ECMO, we performed an additional analysis among patients receiving bridging ECMO while waiting for LTx (Table 3; Supplementary table 3). The additional analysis revealed that the duration of ICU stay and hospitalization were longer and the mortality rates at 6 months and 1 year were significantly higher in the failed weaning group than in the successful weaning group. Univariate analysis revealed significant differences in sex, total fluid intake and transfusion volume during the operation, donor age, and predicted donor/recipient TLC between the two groups. A multivariate analysis including variables identified as significant in the univariate analysis revealed that BMI, transfusion volume >3.8 L, and PaO₂/FiO₂ ratio in the donor lung were independent risk factors for intraoperative ECMO weaning failure among patients receiving bridging ECMO while waiting for LTx.

Table 3. Comparison between bridged ECMO patients weaned successfully from ECMO and those who remained with ECMO after lung transplantation

Variables	ECMO after LTx (n=43)	No ECMO after LTx (n=42)	p-value	OR	CI	p-value
Age, years	56.7 ± 9.9	56.1 ± 8.5	0.773	0.97	0.92-1.02	0.256
Body mass index, kg/m ²	22.6 ± 3.9	20.4 ± 4.3	0.015	1.20	1.04-1.38	0.008
Transfusion > 3.8 liters	23 (53.5)	7 (16.7)	<0.001	9.02	2.61-31.18	0.001
Donor age, years	46.3 ± 11.7	40.3 ± 12.9	0.038	1.03	0.99-1.08	0.162
Donor PaO ₂ /FiO ₂ ratio	411.8 ± 89.4	466.6 ± 98.6	0.009	0.99	0.98-0.99	0.001

Values are expressed as means (standard deviations) or median (interquartile ranges). PaO₂/FiO₂, ratio of arterial oxygen concentration to the fraction of inspired oxygen.

Discussion

Herein, we investigated the risk factors associated with failed weaning from intraoperative ECMO and prognosis among patients undergoing LTx. Our findings indicated that hospitalization periods were longer and survival rates were lower in the failed weaning group than in the successful weaning group. Preoperative factors that increased the risk of weaning failure included older age of the donor, lower PaO₂/FiO₂ ratio of the donor lung, and higher predicted donor/recipient TLC ratio. Intraoperative factors influencing weaning failure after LTx included the duration of operation and transfusion volume. Similar results were obtained in the subgroup analysis of patients who underwent preoperative bridging ECMO.

Conventionally, our center has used ECMO during LTx since March 2013 [6]. The routine use of intraoperative ECMO during LTx allows for controlled perfusion and protective ventilation of the graft during the procedure, thus reducing the risk of later primary graft dysfunction (PGD) [6, 10]. However, extended ECMO is sometimes required in the immediate postoperative period. Several studies have analyzed outcomes among patients with planned continuation of intraoperative ECMO into the postoperative period, which is performed to allow adaptation of the left ventricle to the new loading conditions in patients with severe PH after LTx [9-11, 19]. Results for these patients did not differ from those for patients without severe PH. However, Dell' Amore *et al.* reported a lower incidence of PGD and improved survival in the planned prolonged ECMO group [12]. While prolonged ECMO does not necessarily indicate a poor prognosis, unintended prolonged ECMO may be a marker of recipient status in terms of early graft failure and hemodynamic status [17]. Although several sequential studies have examined survival outcomes after postoperative ECMO, their outcomes have varied [14, 20-22]. Indeed, no studies have identified the preoperative and intraoperative factors associated with the need for extended ECMO following LTx. In our center, Narm *et al.* analyzed data from 74 patients after LTx. Among them,

patients maintained on ECMO for >5 days after surgery exhibited higher mortality during the first year than those maintained on ECMO for <4 days [18]. The authors also noted that increasing donor age, donor PaO₂, and increasing operation time were independent risk factors for ECMO weaning failure after surgery [18].

Our analysis indicated that donor age was significantly correlated with ECMO weaning after surgery. Several studies have also reported that advanced donor age is an independent risk factor for extended ECMO [18, 20]. Theoretically, older lungs may exhibit increased susceptibility to infection and reduced lung function [23]. While recipient age is a well-known prognostic factor for LTx, it did not significantly affect the success of ECMO weaning in our study [24].

Donor PaO₂/FiO₂ ratio is associated with early gas exchange in the recipient [25]. Donor PaO₂/FiO₂ was also a significant risk factor for failed ECMO weaning after surgery. However, there were no differences in allograft ischemic time between the two groups; this factor did not influence the success of ECMO weaning. Although the correlation between ischemic time and pulmonary function or survival remains controversial [26, 27], prolonged graft ischemic time—in older-aged donors—can lead to an adverse interaction [23].

Donor criteria do not include the duration of mechanical ventilation; however, infection in the donor lung has always been considered an absolute contraindication for LTx [25, 28]. Of course, length of intubation is associated with bronchial colonization and predisposes the patient to ventilation-acquired pneumonia [25, 28]. There were no differences in mechanical ventilation between our two study groups, and the duration of ventilation was approximately 7 days.

Surgical variables—long operation time, substantial blood loss due to severe pleural adhesion, delayed harvest team arrival, lengthy hemostasis, and unexpected anatomical or technical difficulties—are adversely related to ECMO weaning. These factors may lead to lower postoperative oxygenation and aggravate pulmonary edema. Geube *et al.* noted an association between transfusion of a higher volume of red blood cells and the development of grade-3 PGD [29].

Historically, size matching has been considered important in LTx [23]. Size mismatch may influence LTx outcomes, and several studies have demonstrated that there are no clinical or functional adverse effects when the donor predicted TCL is between 75% and 125% of the predicted value for the recipient [23]. Here, grafts were larger in the failed weaning group than in the successful weaning group, although this did not significantly influence ECMO weaning.

Patients with severe PH often exhibit significant right ventricular dysfunction, decreased cardiac output, and hemodynamic instability [9]. As in other studies, extended ECMO was more likely to be required in these patients. However, there were no differences in mean pulmonary artery pressure or cardiac function between the two groups in our study (Table 1; Supplementary Table 4).

This study has several limitations, including its single-center design and cohort comprising Asian patients only, limiting the generalizability of the findings. However, since LTx studies have mainly been performed in North America and Europe, our findings may aid in determining the unique features of ECMO weaning following LTx in Asians. Second, this study was retrospective in nature, which may have resulted in selection bias when determining parameters. To our knowledge, no well-designed prospective studies have focused on this topic, and our study includes the largest number of patients who underwent intraoperative ECMO weaning following LTx to date. Thus, our results may aid clinicians in predicting which patients will require ECMO support following LTx. However, well-designed prospective studies are required to verify our findings.

Conclusion

In conclusion, our results indicate that mortality is higher among patients with failed intraoperative ECMO weaning than among those with successful weaning following LTx. Furthermore, both preoperative and intraoperative donor factors, such as donor's age, operation time, and transfusion volume, are significantly associated with failed weaning from intraoperative ECMO after LTx. Therefore, examination of these factors before and during LTx may aid clinicians in predicting prognosis and preparing to manage patients after LTx.

Abbreviations

AUC, Area under the curve

BMI, Body mass index

CI, Confidence interval

ICU, Intensive care unit

OR, Odds ratio

PGD, Primary graft dysfunction

PH, Pulmonary hypertension

ROC, Receiver operating characteristic

TLC, Total lung capacity

Declarations

Ethics approval and consent to participate

This research protocol was approved by the Institutional Review Board of Severance Hospital, South Korea (IRB No. 4-2021-0199), and the study design was approved by the appropriate ethics review boards. The requirement for obtaining patient informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Choi JY designed the report and wrote the paper; Kim SY, Leem AY, Chung KS, Lee SH, Kim EY, Jung JY, Kang YA, Park MS, Kim YS, LeeJG, and Paik HC drafted and revised the manuscript; Lee SH designed the concept and finally approved the paper. All authors have taken due care to ensure the integrity of this work, and this final manuscript has been seen and approved by all authors.

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Figures

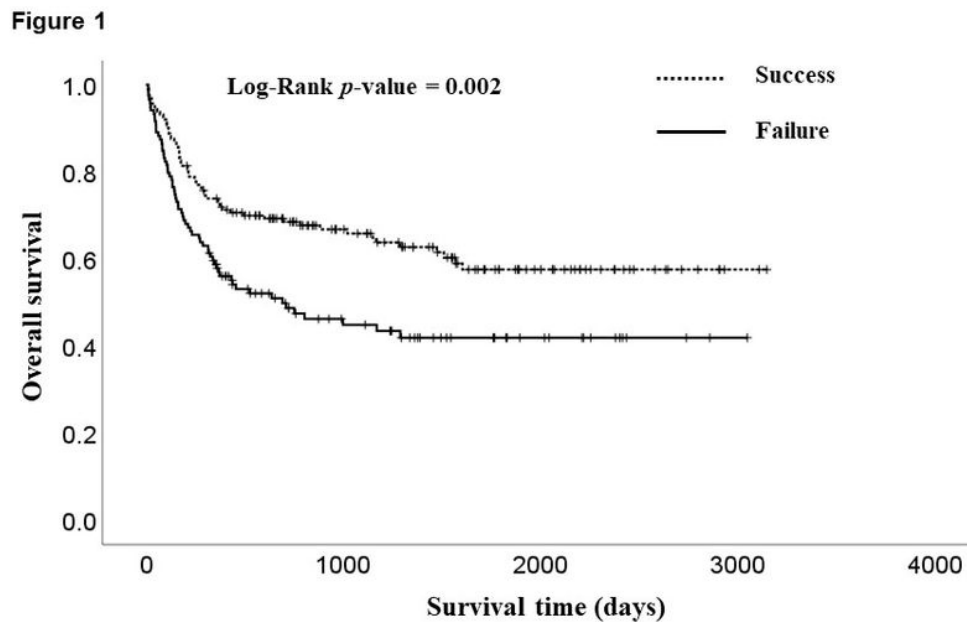


Figure 1

Comparison of overall survival between the failed and successful extracorporeal membrane oxygenation (ECMO) weaning groups. Failed ECMO weaning was significantly associated with poor survival (log-rank p -value=0.002).

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